Chapter 9

General Discussion and Conclusions

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In this thesis, the emphasis is on the different modeling techniques which can be used to estimate the cost-effectiveness of (preventive) interventions aimed at infectious diseases.

As cost-effectiveness analyses consist of both epidemiological and economic aspects the modeling of incidence numbers and costs were firstly addressed both in detail and separately in part I of this thesis (chapters 2 and 3, respectively). In the former, a back-calculation model was designed to estimate the past and future Dutch HIV incidence by using current incidence numbers together with incubation time distributions. This also enabled the prediction of future clinical AIDS cases in the Netherlands. In particular, new incubation time distributions were estimated for persons treated with HAART (Highly Active Anti-Retroviral Therapy) in the Netherlands using a Markov model. Obviously, the introduction of HAART has rendered previously estimated distributions inappropriate [1-3]. Ergo, instead of estimating the epidemiological outcomes of a new medical intervention, here future incidences were predicted assuming that the current course of the disease and treatment effectiveness will not change over time. In chapter 3, a specific type of economic evaluation is discussed for situations in which interventions under consideration can validly be assumed to be equivalent in terms of effectiveness and tolerability, and the analysis basically reduces to a comparison of costs only. This type of analysis is often referred as ”cost-minimization analysis” [4]. A specific difficulty in cost comparisons arises from the fact that distributions of resource use and associated costs are often highly skewed [5]. In the literature several methods for dealing with these skewed distributions were proposed which are reviewed in chapter 3. Here it is concluded that in general the t-test is often a reasonable method in order to compare the costs of alternative strategies. Furthermore, if individual data on resource use and costs are available, parametric modeling is indicated as an appropriate method for comparing costs and resource use. In annex 1 we applied parametric modeling in order to examine the difference in costs between two antibiotics, teicoplanin and vancomycin, in the treatment of gram-positive infections from the health-care provider’s perspective.

Possible Consequences of Neglecting Herd-Immunity Effects

The remainder of this thesis fully concentrates on the different types of models that can be used to predict the health and economic impact of interventions in the specific field of infectious diseases. The main focus is on the distinction between static and dynamic approaches. As mentioned in the introduction, in dynamic models the force of infection (FOI)

depends on the number of infectious individuals in the population whereas in static models this parameter is assumed to be fixed [6-8]. Different types of static and dynamic models are discussed in respectively part II and part III of this thesis. I will start with part III below and will return to part II in the latter part of this section.

In chapter 6 (part III) we designed a dynamic SIS (Susceptible-Infected-Susceptible) model to estimate the cost-effectiveness of a one-off systematic *Chlamydia trachomatis* (CT) screening program in the Netherlands. Furthermore, using the same dynamic model, in chapter 7, further research was performed to assess the most cost-effective screening frequency. The dynamic model we designed was a so called SIS (Susceptible-Infected-Susceptible) model. Here, as no immunity was assumed, the population was made to flow between the mutually exclusive compartments: S (Susceptible), I (infected) and S (Susceptible). This model is deterministic and population based with the flow between the different compartments being described by a set of coupled ordinary differential equations. These kinds of deterministic models a have been most commonly used for dynamically modeling infectious diseases. In chapter 6 we showed that most (>90%) of the averted costs and averted complications due to CT screening resulted from the indirect herd immunity effects. In a static model all these benefits would have been neglected. Notably, other authors have often applied a static design in analyzing cost-effectiveness of CT screening [9]. Accordingly, the modeling approach can have a major impact on the outcomes and, even more important, on the decision whether or not to implement such a screening program. Within a time period of 20 years a one-off CT screening program was estimated cost-saving using the dynamic model in chapter 7, while the cost-effectiveness of the program is estimated at □68,000 per QALY when a static approach would have been used. This means that if a cost-effectiveness threshold of □20,000 per QALY is assumed the program should not be implemented from a health economic point of view when, incorrectly, a static approach was applied. As a CT infection is transmitted through sexual intercourse and is not solely restricted to certain groups in the population, the only appropriate method for fully predicting all consequences of a screening program would be a dynamic approach that also takes the indirect effects into account.

Researchers often argue that using a statistic model instead of a dynamic one always lead to an underestimate of the incremental cost-effectiveness ratio (ICER) as the decrease in the FOI is omitted. In other words, if an intervention is estimated cost-effective using a static approach it will be even more cost-effective when the indirect herd immunity effects are taken into account. However, the decrease in FOI can not only have beneficial effects but also have detrimental effects. Although in general an intervention will lead to a decrease

in total incidence of the infection in the population it could cause an increase in absolute incidence numbers in certain sub-groups. Brisson et al [7] showed that, using a dynamic model, routine infant varicella vaccination could be able to cause the average age at infection to rise, resulting in an absolute increase in the number of adult cases. Static models on the other hand are not able to predict this absolute increase. As severity (i.e. mortality and morbidity) of the diseases increases with age a static approach could lead to a more favorable cost-effectiveness compared to a dynamic approach.

This shift in age accompanied by an increase in complications in certain age groups is also seen in chapter 8 of this thesis. Here we designed a stochastic individually based DES (Discrete Event Simulation) model to estimate the cost-effectiveness of adolescent pertussis booster vaccination. Although the total incidence decreased in the population as a result of adolescent vaccination, the absolute number of recidive infections in the older age groups (i.e. 20-49 and 50-74 years) increased. Accordingly, the total costs associated with pertussis complications in these age groups increased compared to the current situation of no adolescent vaccination. Yet, an age shift can also have beneficial effects if disease severity decreases with age (e.g. measles in developed countries). So, omitting an age shift through static modeling can lead to both more positive and more negative results compared to dynamic models, depending on the relative severity of the disease in different age groups.

Furthermore, Welte et al [10] compared a static model and dynamic stochastic network simulation model for estimating the cost-effectiveness of an opportunistic CT screening program. They showed that both models lead to very different ICERs, but perhaps even more importantly from a decision maker's point of view, the static model also identified the incorrect optimal age group for screening. Summarizing, the assumption that neglecting the indirect herd-immunity effects only yields conservative results is wrong, as it also may result in: (i) implementing an intervention in the wrong target group; or (ii) in a too favorable ICER due to the omission of negative effects due to a shift in incidence towards older age groups where the disease is more harmful.

The Current Role of Dynamic Modeling in Guidelines for Health-Economic Research

Economic evaluations of interventions aimed at transmissible infectious diseases should by necessity be based on modeling, as clinical trials do not provide a good estimate of the total effects of such an intervention. Clinical trials provide an estimate of the *efficacy* (i.e. direct effects) but not of the *effectiveness* (i.e. direct and indirect effects). As mentioned above, in

order to make reliable health policy decisions, if present, the indirect herd-immunity effects should also be taken into account in cost-effectiveness analyses. To ensure the quality of economic evaluations, several national and international guidelines have been formulated for health-economic and pharmacoeconomic research by now [11]. As modeling is widely used in economic evaluations of pharmaceuticals and other health-care interventions specific guidelines on modeling have been published and are often included in the general guidelines for economic research. Unfortunately, these guidelines on modeling most often only apply for non-infectious-disease related health care interventions [12]. Therefore, additional specific guidelines are needed for economic evaluations of interventions directed at infectious diseases. Obviously, modeling of infectious diseases most importantly requires different and more complex modeling techniques to capture the indirect herd-immunity effects.

In the Netherlands, the first national guidelines for pharmacoeconomic research formulated by the ”College Voor Zorgverzekeringen” (CVZ) were published in 1999 [13]. Recently in 2006, these national guidelines were updated and now consist of 11 guidelines [14]. One of these guidelines discusses modeling within pharmacoeconomic analyses. However, nothing else than: “the model must be as simple as possible, and obviously it must include all the most important processes” is mentioned about model structures in general [14]. Notably, nothing specifically is written about the modeling of infectious diseases in particular. In practice, the Dutch drug-reimbursement authority (i.e. CVZ) will not even assess pharmacoeconomic studies that include dynamic modeling. CVZ demands economic models that are easy to understand, highly transparent and which are designed in either Excel [Microsoft, Redmond, US] or TreeAge [TreeAge Software, Inc., Williamstown, US] software packages. However, those software packages are not suitable for the dynamic modeling of infectious diseases. Notably, two recent submissions for reimbursement on both available HPV-vaccines to CVZ were both denied based on lack of transparency of the health-economic models [15]. Note that in both cases highly complex, though not even fully dynamical, models were used.

As discussed above t*ransparency* is explicitly mentioned as a requirement in the first sentence of the guideline: “In order to be able to support decision making, the model must be transparent” [14]. One might expect that CVZ would not qualify dynamic models as *transparent* as they are often considerably complex and modeled in specific statistical or mathematical software packages. Furthermore, to fully grasp all aspects of such a dynamic model one certainly has to put much time and effort in it compared to decision trees or Markov models. I would feel however that in order to make reliable decisions, the first requirement should always be that decisions are based on cost-effectiveness outcomes that are trustworthy. If the intervention under consideration is aimed at an infectious disease

and influences the transmission of it, herd-immunity effects should not be neglected as otherwise the outcomes will certainly not reflect reality. Summarized, although it increases model's complexity, in my opinion herd-immunity refers to such an 'important process' that according to the guideline obviously must be included in the model [14]. Furthermore, it is important to realize that an increase in the model's complexity will not per definition result in a decrease in transparency. In other words it is a misconception to think that the time and effort spend in fully understanding a model is directly related to the transparency as this depends for a major part on the type of model and the reporting of it.

Recommendations for Adjustment of the National Guidelines for Pharmacoeconomic Research in Order to Improve Medical Decision Making Within the Field of Infectious Diseases

I would strongly advise the Dutch drug-reimbursement authority to add specific guidance on the modeling of infectious diseases in their guidelines for pharmacoeconomic research in order to adequately assist medical decision making. This might allow appropriate and valid (re-)assessments of upcoming new anti-infective agents and vaccines (HPV, rotavirus, varicella and zoster vaccines). To support this process I will finish this thesis with a guide on choosing the appropriate health-economic model for economic evaluations on interventions for infectious diseases. Although several decisions have to be made in modeling infectious diseases, the primary and most important one is the choice to use either a dynamic or a static model. Unfortunately, there is not one type of model that is suitable for all situations. This decision depends on the specific pathogen, the specific intervention, the specific target population and the perspective of the economic analysis. Under specific conditions static models provide an adequate description of the cost-effectiveness of interventions aimed at infectious diseases, in particular if (i) there is no transmission between humans (e.g. rabies and tetanus); (ii) if the intervention under consideration has no or a neglible effect on the FOI in the population. In other words the intervention does not induce herd immunity. First, this comprehends interventions which have no influence on the susceptibility to infection and transmission of the infection. In general, one can say that prophylactic interventions will affect the FOI whereas therapeutic interventions will not. Furthermore, selective interventions in small groups which do not contribute significantly to the transmission of the infection, such as vaccination for hepatitis A in travellers from low to high endemicity areas and influenza vaccination in elderly; and (iii) in the specific situation where the decision maker is solely interested in the direct health and economic outcomes in the target group that re-

ceives the intervention. For instance analyses carried out from a payer's perspective match this description. Figure 1 graphically depicts the flowchart to help determine the appropriate modeling approach (i.e. static or dynamic).

In part II of this thesis, examples were given of latter two conditions were static models are considered suitable to estimate the cost-effectiveness. First, in chapter 4 the cost-effectiveness of itraconazole prophylaxis in neutropenic patients treated for haematological malignancies was estimated. A probabilistic decision tree model was designed with the transition probabilities being extracted from two meta-analyses. A decision tree was designed as the complications (i.e. invasive fungal infections) occurred only within the short neutropenic period, implicating that the time factor is not crucial which makes Markov modeling unnecessarily complex [4, 16-21]. Here, a static approach was justified as the prophylactic intervention did not affect the FOI. In other words, the probability of acquiring an invasive fungal infection for those who do not receive prophylaxis will not change as a result of providing antifungal prophylaxis to others. These patients only acquire an invasive fungal infection if they are already immunocompromized as result of transplantation or disease (e.g. leukemia and AIDS). Also, as these bedridden patients will not have close contacts with other patients, susceptibility for invasive fungal infection is not influenced by prophylaxis. Furthermore, often the patient is already a carrier of the fungus which he/she acquired in the past (e.g. *Candida* species), which is not harmful for healthy persons, or receives the fungus through other routes (e.g. *Aspergillus* species living in buildings).

In chapter 5 we designed a probabilistic Markov model to estimate the cost-effectiveness of a potential future *Helicobacter pylori* (HP) vaccine for the Dutch situation. Here, a Markov model was chosen for modeling long term effects as the risk of acquiring both gastric cancer and peptic ulcer continues over a life-time period [4, 16, 17, 19-21]. It concerned a cohort study in which interest was only in the health benefits and economic consequences in the birth cohort to be vaccinated (i.e. target group). As both a high vaccine effectiveness was assumed and re-infection to be of no interest (assuming the prophylactic HP vaccine to provide lifelong protection), indirect effects in the target group due to vaccination were negligible and therefore in this particular study the use of a static approach was legitimized. Obviously, if the effectiveness was assumed considerable lower or if the vaccine was not assumed to provide lifelong protection and affects the transmission in the population, a dynamic approach would be preferable as due to indirect herd-immunity effects the (re-) infection rate would probably change over time in the target population. However, as no HP vaccine has been licensed yet, the coverage, effectiveness, duration of protection and the influence on the transmission remain uncertain [22].

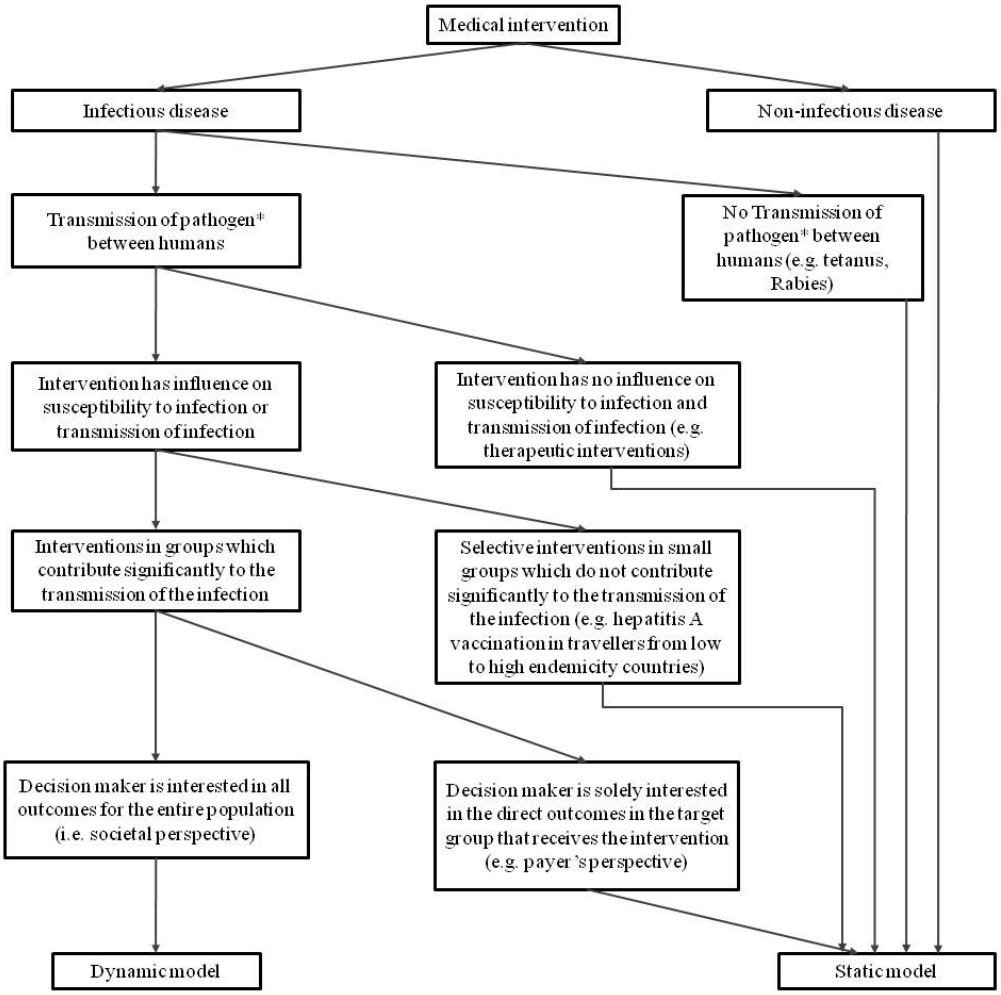

Figure 1. Guide on choosing the appropriate modeling approach. Pathogen are bacteria, viruses and fungi.

After choosing either a dynamic or a static approach to model cost-effectiveness one has to define the specific type of model, with several options being available for both approaches. Regarding static modeling the two most used types (i.e. decision trees and Markov models) together with their use under specific conditions were discussed above. Dynamic models can be roughly divided into stochastic and deterministic models of which two examples were given in chapter 8 and chapter 6, respectively. In general, when the population is large enough and the infection is not close to eradication, one is not better than the other. However, stochastic dynamic models could be more suitable to model infections in small popula-

tions or which emerge in a small fraction of the population (e.g. pandemic influenza) as in these situations ”chance” plays an important role in the spread of the disease. For example, in pandemic influenza it might be merely luck or misfortune whether the occurrence of a new variant in a small number of humans really takes off to become a full-scale pandemic [23]. Furthermore, note that within in a dynamic model an infection will never totally vanish as always a small fraction will remain infected.

Conclusion

In conclusion, in this thesis the importance of dynamic modeling to estimate the cost-effectiveness of interventions aimed at infectious diseases is stressed. However, currently, as in many other countries, nothing is written down on the modeling of infectious diseases in the Dutch national guidelines for pharmacoeconomic research. I think it is crucial that national guidance on this topic is developed. To help this development, I ended this thesis with a potential guide on choosing the appropriate model under different circumstances. In my opinion, in order to support evidence-based medical decision making, a guide on modeling infectious diseases (inclusive the role of dynamic models) should be included in national guidelines. My guide generally corresponds with the guidelines on the modeling of infectious diseases published in the recently developed WHO guide for standardization of economic evaluations of immunization programmes [24]. Although the WHO guidelines are more comprehensive, the above guidance covers the most important points of interest. At the moment dynamic models do not play any role in assessments by the Dutch drug-reimbursement authority, also because they are seen as non-transparent ”black-boxes”. I do note that in recent years more user-friendly software packages for dynamic modeling of infectious diseases have become available. These include for example: ModelMaker [ModelKinetix, Wallingord, UK] and Berkely Madonna [University of Berkely, California, US]. These packages certainly allow the development of transparent and very assessable models. I expect reimbursement authorities to soon embark on these models as they are sometimes indispensable in the modeling of drugs and vaccines for infectious diseases. I also think that this is necessary as reliable health policy decisions on infectious diseases control cannot be made without valid models that treat infectious diseases according to their unique nature of being INFECTIOUS!

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